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As a follow-up to the comprehensive work on solid cancer incidence in the Life Span Study (LSS) cohort of atomic bomb survivors between 1958 and 1998, we report here on updated radiation risk estimates for upper digestive tract cancers. In this study, we added 11 years of follow-up (1958–2009), used improved radiation dose estimates, considered effects of smoking and alcohol consumption and performed dose-response analyses by anatomical sub-site. In examining 52 years'worth of data, we ascertained the occurrence of 394 oral cavity/pharyngeal cancers, 486 esophageal cancers and 5,661 stomach cancers among 105,444 subjects. The radiation risk for oral cavity/pharyngeal cancer, other than salivary gland, was elevated but not significantly so. In contrast, salivary gland cancer exhibited a strong linear dose response with excess relative risk (ERR) of 2.54 per Gy [95% confidence interval (CI): 0.69 to 6.1]. Radiation risk decreased considerably with increasing age at time of exposure (–66% per decade, 95% CI: –88% to –32%). The dose response for esophageal cancer was statistically significant under a simple linear, linear-quadratic and quadratic model. Both linear-quadratic and quadratic models described the data better than a simple linear model and, of the two, the quadratic model showed a marginally better fit based on the Akaike Information Criteria. Sex difference in linear ERRs was not statistically significant; however, when the dose-response shape was allowed to vary by sex, statistically significant curvature was found among males, with no evidence of quadratic departure from linearity among females. The risk for stomach cancer increased significantly with dose and there was little evidence for quadratic departure from linearity among either males or females. The sex-averaged ERR at age 70 was 0.33 per Gy (95% CI: 0.20 to 0.47). The ERR decreased significantly (–1.93 power of attained age, 95% CI: –2.94 to –0.82) with increasing attained age, but not with age at exposure, and was higher in females than males ($P = 0.02$). Our results are largely consistent with the results of prior LSS analyses. Salivary gland, esophageal and stomach cancers continue to show significant increases in risk with radiation dose. Adjustment for lifestyle factors had almost no impact on the radiation effect estimates. Further follow-up of the LSS cohort is important to clarify the nature of radiation effects for upper digestive tract cancers, especially for oral cavity/pharyngeal and esophageal cancers, for which detailed investigation for dose-response shape could not be conducted due to the small number of cases.

INTRODUCTION

Moderate-to-high doses of ionizing radiation are known to increase the risk of cancers of the upper digestive tract (i.e., oral cavity and pharynx, esophagus and stomach) (*1*–*3*), but there is less evidence for risk at lower doses. One of the key sources of quantitative estimates of cancer risk after exposure to low-linear energy transfer (LET) radiation in humans is the Life Span Study (LSS), a cohort of Japanese atomic bomb survivors who have been followed for cancer incidence since 1958. A previously published analysis of solid cancers from the LSS with follow-up through 1998 reported elevated risk for each of the upper digestive sites (*4*). The sex-averaged excess relative risks (ERR) at age 70 years after exposure at age 30 years were 0.39 per Gy [90% confidence interval (CI): 0.11 to 0.76] for cancers of the oral cavity and pharynx, 0.52 per Gy (90% CI: 0.15 to 1.0) for esophageal cancer and 0.34 per Gy (90% CI: 0.22 to 0.47) for stomach cancer.

In studies other than the LSS, the association between radiation exposure and risk of digestive tract cancers has been examined, with mixed results. X rays and gamma rays are reported as agents with sufficient evidence of

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carcinogenicity for salivary gland cancer in IARC monographs (*5*). However, the radiation risk for oral cavity and pharyngeal cancer combined is unclear: significant risk for cancer of the oral cavity was not observed in the cohort study of Techa River residents (*6*), while the INWORKS study of nuclear workers showed positive risk estimate for cancer of the oral cavity (*7*). Meanwhile, significant radiation risk for esophageal cancer has been observed in several studies of populations exposed to radiation (*6, 8–10*). In addition, studies of patients who received radiation therapy (*11–14*) showed significantly increased risk of stomach cancer. The Mayak Worker Cohort showed marginally significant increase of radiation-related stomach cancer risk (*10*). Due to the higher incidence rate of stomach cancer in Japan compared to European and American countries (*15*), the study of atomic bomb survivors, with its large number of cases, has provided important information on radiation risk.

Cigarette smoking and alcohol consumption are major etiologic factors for upper digestive cancers (*16*). Cigarette smoking is an established risk factor for oral cavity and pharyngeal cancers, esophageal cancer and stomach cancer. Alcohol consumption is known to increase the risk of oral cavity, pharyngeal and esophageal cancer, but its relationship with stomach cancer remains controversial. One of two large meta-analyses showed a significant positive association with risk of stomach cancer but the other study did not (*17, 18*). Most previous studies of the LSS have not accounted for risk factors other than radiation.

In this work, we incorporated an additional 11 years of follow-up since the previously published comprehensive study (*4*) (totaling 52 years, between 1958 and 2009) and used improved radiation dose estimates to conduct dose-response analyses for cancers of the oral cavity and pharynx, esophagus and stomach while adjusting for smoking history and alcohol consumption. The substantially increased number of cases allowed us to improve radiation risk estimates and examine risk modification by age and sex, as well as explore radiation effects by anatomical sub-site for specific cancers in greater detail. Additionally, the incorporation of lifestyle data allowed us not only to adjust the baseline rates for smoking and alcohol intake, but also to consider the nature of their joint effects with radiation and investigate radiation effect modification by these factors.

METHODS

Study Population

This work is part of a series of published studies on cancer incidence among Japanese atomic bomb survivors over the period of 1958–2009 (*19–21*). The methods are described in detail elsewhere (*22*). In brief, the LSS cohort of 120,321 participants comprises 94,000 atomic bomb survivors who were in Hiroshima or Nagasaki during the bombings (and lived in either city at the time of the 1950 National Census), as well as 26,580 persons who were not in either city (NIC) during the bombings (and were identified in 1950–1953). Analyses of incidence data are limited to the members of the cohort who were alive and not known to have a diagnosis of cancer prior to January 1, 1958. After exclusion of those who had died or were diagnosed with cancer prior to that time (n = 8,317), those who could not be traced (n = 86), one duplicate (n = 1) and those for whom individual radiation doses could not be estimated (n = 6,473), the analysis cohort included 105,444 individuals.

Case Ascertainment

Information on cancer incidence was primarily obtained from the Hiroshima and Nagasaki cancer registries. In these analyses, we focused on cancers of the oral cavity and pharynx (ICD-O-3 topography codes: C00-C14), esophagus (C15) and stomach (C16). Analyses by anatomical sub-sites were also conducted for oral cavity and pharyngeal cancer: salivary gland cancer (C079-C089) and other than salivary gland cancer (C00.0-C06.9, C09.0-C14.8); for esophageal cancer: upper/middle part (C150, C151, C153, C154) and lower part (C152, C155); and for stomach cancer: cardia (C160), upper/middle (C162) and lower stomach (C163, C164). Because coverage of the Hiroshima and Nagasaki cancer registries is limited to Hiroshima Prefecture and Nagasaki Prefecture and individual residence history data are not available for most cohort members, cases were limited to those diagnosed in the tumor registries' catchment areas, and person-years were adjusted for migration rates into and out of the catchment areas. Migration rates were derived from the observed migration rates of participants in the Adult Health Study (AHS), a sub-cohort of the LSS who undergo biennial clinical examinations (*23*).

Exposure Assessment

Radiation effects were assessed using individual weighted organ-specific dose estimates, calculated as the sum of gamma-ray dose and ten times neutron dose. Revised dose estimates (DS02R1) were calculated from Dosimetry System 2002 (DS02) (*24*), based on survivors' distance from the hypocenter and shielding at the time of the bombings (*25*). For survivors with total shielded kerma >4 Gy, the doses were truncated so that the total shielded kerma dose was 4 Gy. As in all recent LSS reports, individual dose estimates were adjusted for dose uncertainty arising from measurement errors with an assumed coefficient of variation of 35% (*26*). Analyses of cancers of the oral cavity used eye dose as a surrogate, while analyses of esophageal and stomach cancer used stomach dose.

Information on smoking habits and alcohol consumption was obtained from three AHS interviews (conducted in 1963, 1965 and 1968) and four LSS mail surveys (conducted in 1965, 1969, 1978 and 1991). Smoking and alcohol data were available for approximately 60% of the cohort members. More details about these data are available elsewhere (*22*).

Statistical Analysis

Excess relative risks (ERRs) for the cancers of interest were estimated using Poisson regression models. The primary radiation ERR (ERR_{rad}) model used herein can be expressed as:

$$\lambda = \lambda_0^*(c, s, b, a, nic, z_0)[1 + ERR_{rad}(d, s, e, a, t, z_1),$$

where the baseline rates ($\lambda_0^*(c, s, b, a, nic, z_0)$), which describe the rates among people with zero radiation dose, were allowed to depend on sex (s), attained age (a), in city or not in city at the time of the bombings (nic) and, as necessary, on city (c), birth year (b) and other factors (z_0) such as alcohol consumption or smoking habits. The excess relative risk (ERR_{rad}) associated with radiation dose (d) was allowed to depend on sex, age at exposure (e), attained age, time since exposure (t) and other factors (z_1). The ERR_{rad} was described using models that can be expressed as:

$$\rho_s(d)\varepsilon(e,a,t,z_1),$$

where $\rho_s(d)$ describes the possibly sex-dependent, dose-response shape and $\varepsilon(e,a,t,z_1)$ describes radiation effect modification, usually taken as a log-linear function of the variables of interest. An indicator for subjects with total shielded kerma of >4 Gy was included as an effect modifier, allowing us to estimate the dose-response parameters separately for subjects with and without truncated doses. We considered various dose-response functions including: linear ($\beta_1 d$), linear-quadratic ($\beta_1 d + \beta_2 d^2$) and categorical:

$$\sum_i \beta_i I(D_i \le d < D_{i+1}),$$

where D_i is an ordered set of dose cut-off points (0, 0.005, 0.02, 0.04, 0.06, 0.08, 0.1, 0.125, 0.150, 0.175, 0.2, 0.25, 0.3, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2 and 3 Gy) and I is an indicator function. If adding a quadratic term to the linear dose-response model resulted in the improved fit, we also considered a quadratic ($\beta_1 d^2$) model. The dose-response parameters were allowed to differ by sex.

Results of our primary analyses are presented after adjustment for smoking history and alcohol consumption when these were significantly associated with cancer risk. We characterized the joint effects of radiation, smoking and alcohol consumption using either simple multiplicative ERR models, $\lambda_0(1 + ERR_{smk})(1 + ERR_{alc})(1 + ERR_{rad})$ or simple additive ERR models, $\lambda_0(1 + ERR_{smk} + ERR_{alc} + ERR_{rad})$. Unless otherwise noted, radiation risk estimates were based on multiplicative models. For comparison with earlier LSS reports (*4*) we also show results without adjustment for smoking history and alcohol consumption. Detailed description of the smoking history data in the LSS and the form of the smoking ERR can be found elsewhere in recently published work (*19, 22*). In brief, ERR_{smk} was described as a function of smoking intensity (packs per day), time-dependent smoking duration, and for past smokers, years since smoking cessation with sex- and time-dependent indicators of unknown smoking status (see additional details in the Supplementary Information, http://dx.doi.org/10.1667/RR15386.1.S1).

The ERR associated with alcohol consumption (ERR_{alc}) was modeled as a function of the individual average weekly consumption over questionnaires expressed in grams (g) of ethanol per week. Computation of alcohol consumption was based on the assumption that one drink contained 14 g of ethanol (*27*). Alcohol consumption was treated as unknown prior to the date (if any) at which this information was first obtained. As with ERR_{smk}, sex-specific time-dependent indicators of unknown alcohol consumption were included in the model.

Joint analyses (*28*) were conducted to explore heterogeneity in radiation effect estimates by anatomic sub-site for oral cavity/pharyngeal cancer, esophageal cancer and stomach cancer.

We did not explicitly fit excess absolute rate (EAR) models to the data except for stomach cancer; instead, ERR models were used to construct EAR estimates for selected exposure scenarios.

RESULTS

Between 1958 and 2009 there were a total of 394 cancers of the oral cavity or pharynx, 486 esophageal cancers and 5,661 cases of stomach cancer, which corresponded to 1.7%, 2.1% and 25% of all solid cancers ascertained in the LSS during this period, respectively. As expected, based on a general Japanese population of comparable age and gender distribution, stomach cancer was the most common cancer in the LSS cohort. Table 1 provides information on the number of cases and crude rates for each upper digestive tract cancer site separately for men and women by city, age at diagnosis, amount smoked (pack-years) and average alcohol consumption.

Oral Cavity and Pharyngeal Cancers

Cancers of the tongue, gum and mouth accounted for more than one half of 394 cancers in this group (Appendix Table A1, upper part). Overall, histological type was known for 92% of the cancers. Approximately 83% of cancers with known histology were squamous cell carcinomas and 12% were adenocarcinomas. Nearly all squamous cell carcinomas (97%) were oral or pharyngeal cancers and most of adenocarcinomas (66%) were salivary gland cancers.

For all cancers of the oral cavity/pharynx combined, we observed a statistically significant linear dose response ($P = 0.01$). The fit of a linear-quadratic model was not significantly better ($P = 0.25$) than that of the simple linear model. The minimally adjusted (attained age, sex, birth year, city, exposure status) simple linear ERR per Gy estimate of 0.47 (95% CI: 0.10 to 0.97) was slightly larger than the corresponding estimate of 0.39 for follow-up through 1998 (*4*). Examination of risk by major sub-sites of oral/pharyngeal cancers suggested the strongest radiation effect was for cancers of the salivary gland and, therefore, all further results are presented separately for salivary gland cancers and other oral/pharyngeal cancers combined.

Oral and Pharyngeal Cancers other than Salivary Gland

Baseline rates. Overall, there were 344 cancers in this sub-group, including 232 oral cancers (119 tongue cancers, 91 gum cancers and 22 others), 107 pharyngeal cancers and five other/unspecified cancers. The baseline rates were approximately doubled for every decade of increase in age for both sexes and peaked between the ages of 75–79 years for males (Supplementary Fig. S1; http://dx.doi.org/10.1667/RR15386.1.S1). For the same attained age, the earlier birth cohorts had higher incidence rates than later birth cohorts, while for the same attained age and year of birth males had approximately three times higher rates than females (P value for sex difference < 0.001). Both smoking history and alcohol consumption had significant effects on the baseline rates in separate analyses. When included into the same model simultaneously, the effect of smoking remained significant ($P < 0.001$), but the effect of alcohol consumption became borderline ($P = 0.05$). Once adjusted for smoking and alcohol, the baseline rates in males and females were not significantly different ($P = 0.58$). Details concerning the baseline rate model are available in the Supplementary Table S1.

Radiation effects. We observed an elevated radiation-related risk, which was statistically insignificant (Table 2, upper panel; Fig. 1A). The estimate of the ERR was 0.24 per Gy (95% CI: –0.08 to 0.72, $P = 0.18$) based on a simple linear model. Adjustment for smoking and alcohol consumption had little effect on the estimate of radiation ERR. The final preferred model for oral/pharyngeal cancers

TABLE 1
Cases and Crude Rates for Upper Digestive Tract Cancers in the LSS by Sex between 1958 and 2009

		Male					
		Oral cavity and pharynx		Esophagus		Stomach	
	Person-years	No. of cases	Crude rate per 10^5	No. of cases	Crude rate per 10^5	No. of cases	Crude rate per 10^5
City							
Hiroshima	807,736	166	20.6	297	36.8	2,316	286.7
Nagasaki	334,498	70	20.9	97	29.0	774	231.4
Age at diagnosis (years)							
<40	292,684	6	2.0	1	0.3	53	18.1
40–	187,459	14	7.5	9	4.8	150	80.0
50–	229,593	53	23.1	63	27.4	470	204.7
60–	238,160	84	35.3	152	63.8	1,038	435.8
70–	143,799	62	43.1	124	86.2	982	682.9
≥80	50,542	17	33.6	45	89.0	397	785.5
Smoking (pack-years)							
Unknown	703,265	99	14.1	167	23.7	1,208	171.8
0	65,785	10	15.2	10	15.2	190	288.8
1–29	150,711	32	21.2	39	25.9	463	307.2
30–49	155,771	59	37.9	100	64.2	738	473.8
≥50	66,702	36	54.0	78	116.9	491	736.1
Alcohol intake (ethanol g/week)							
Unknown	808,936	130	16.1	218	26.9	1,807	223.4
0	63,421	12	18.9	14	22.1	218	343.7
0–190	135,837	39	28.7	52	38.3	534	393.1
200–390	66,703	22	33.0	45	67.5	270	404.8
≥400	67,338	33	49.0	65	96.5	261	387.6
Total	1,142,234	236	20.7	394	34.5	3,090	270.5

Note. Person-years shown are rounded; the sum of the numeric totals does not necessarily equal the total in lowest row.

included a linear dose-response function with effect modification by total shielded kerma >4 Gy, and multiplicative joint effect with smoking and alcohol consumption.

Cancer of the Salivary Gland

Baseline rates. There were 50 salivary gland cancers. The baseline rates increased in proportion to attained age and were approximately three times higher among males than females, with no indication of statistically significant effects of birth cohort, smoking history or alcohol consumption (Supplementary Table S2; http://dx.doi.org/10.1667/RR15386.1.S1).

Radiation effects. In a simple linear dose-response model, we observed a significant radiation effect with an estimated ERR of 2.54 per Gy (95% CI: 0.69 to 6.1, $P = 0.002$; Table 2, lower panel). Inclusion of a quadratic dose term did not improve the model fit ($P > 0.5$). The ERR declined significantly with increasing age at exposure ($P = 0.001$) with little evidence of statistically significant effects of

TABLE 2
Radiation Parameter Estimates for Oral/Pharyngeal Cancers[a] and Salivary Gland Cancer

	Simple linear ERR[b]	Linear ERR, adjusted for smoking and alcohol	Linear ERR with effect modifier
Oral/pharyngeal cancer[a] (n = 344)			
ERR/Gy	0.24 (–0.08, 0.72)[c]	0.26[d] (–0.08, 0.75)	
AIC[e]	32.2	0	
Salivary gland cancer (n = 50)			
ERR/Gy	2.54 (0.69, 6.1)	-	0.72[d] (0.04, 3.20)
Age at exposure (% change per decade)	-	-	–66% (–88%, –32%)
AIC[e]	8.3	-	0

[a] Excluding salivary gland cancer.
[b] Excess relative risk.
[c] 95% Confidence interval.
[d] The recommended model for oral/pharynx cancer (excluding salivary gland cancer) is $(1 + \beta d * \exp(\phi I(K > 4)))(1 + ERR_{smk})(1 + ERR_{drk})$ and the recommended model for salivary gland cancer is $1 + \beta d * \exp\left(\delta_2\left(\frac{e-30}{10}\right) + \phi I(K > 4)\right)$, where d is radiation dose, I is an indication function, K is total shielded kerma, e is age at exposure and β, ϕ and δ are regression coefficients.
[e] Akaike Information Criterion (AIC) difference from model with lowest AIC.

TABLE 1
Extended.

	Female					
	Oral cavity and pharynx		Esophagus		Stomach	
Person-years	No. of cases	Crude rate per 10^5	No. of cases	Crude rate per 10^5	No. of cases	Crude rate per 10^5
1,385,540	111	8.0	68	4.9	1,963	141.7
551,726	47	8.5	24	4.3	608	110.2
353,393	5	1.4	0	0.0	66	18.7
298,867	14	4.7	5	1.7	134	44.8
385,173	28	7.3	5	1.3	339	88.0
413,004	31	7.5	27	6.5	641	155.2
313,324	44	14.0	22	7.0	805	256.9
173,496	36	20.7	33	19.0	586	337.8
1,113,220	65	5.8	41	3.7	1,236	111.0
694,422	79	11.4	39	5.6	1,070	154.0
108,558	9	8.3	9	8.3	203	187.0
18,095	4	22.1	3	16.6	53	292.9
2,971	1	33.7	0	0.0	9	302.9
1,071,800	65	6.1	38	3.5	1,188	110.8
668,340	66	9.9	40	6.0	1,036	155.0
183,633	25	13.6	11	6.0	322	175.3
9,818	1	10.2	1	10.2	23	234.3
3,669	1	27.3	2	54.5	2	54.5
1,937,266	158	8.2	92	4.7	2,571	132.7

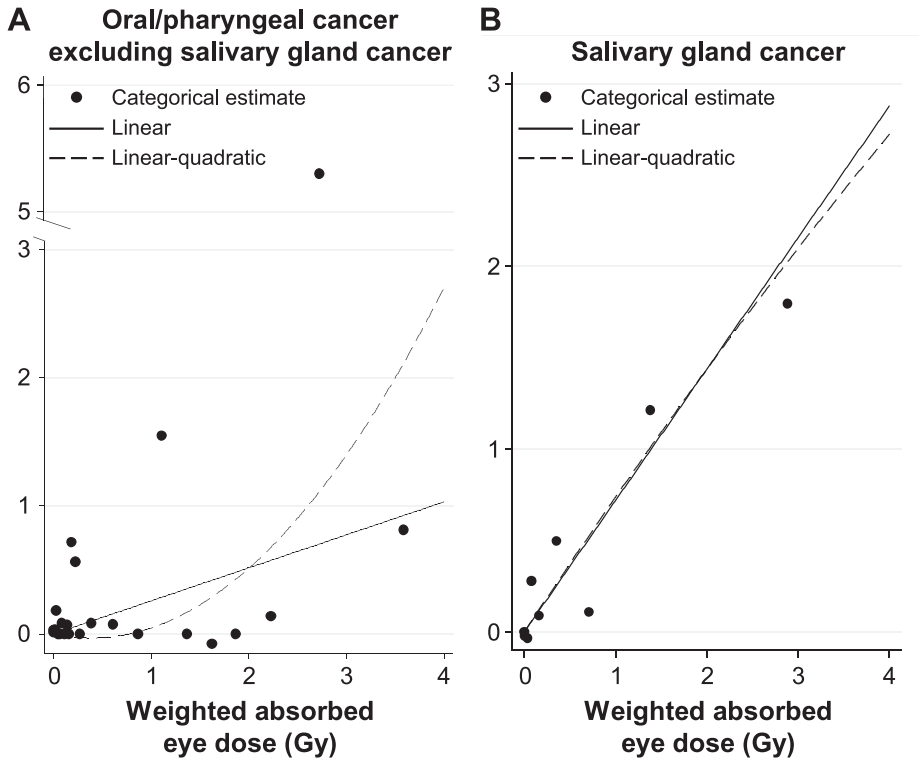

FIG. 1. Dose-response plots for all cancers of oral cavity/pharynx (excluding salivary gland) (panel A) and salivary gland cancers (panel B). Note that y axes are on different scales. Fitted linear (solid line) and linear-quadratic (dashed line) radiation dose-response functions are shown for cancers of the oral cavity and pharynx (excluding salivary gland) (panel A) and salivary gland (panel B). The plot also includes categorical estimates of the excess relative risk (ERR) (points). Separate estimates for the subjects with unshielded kerma >4 Gy are not shown because the number of cases for oral cavity/pharyngeal cancer (excluding salivary grand cancer) and salivary gland cancer among the subjects with unshielded kerma >4 Gy were 1 and 0, respectively.

TABLE 3
Observed and Fitted[a] Cancers of the Salivary Gland by Dose Category

Dose (Gy)	People	Person-years[b]	Cases	Background[c]	Radiation[b]
<0.005	59,840	1,755,781	22	21.8	0.0
–0.1	27,203	798,493	12	9.7	1.1
–0.2	5,690	166,140	3	2.1	1.0
–0.5	6,131	176,597	6	2.2	2.4
–1	3,574	101,067	1	1.2	2.6
–2	2,038	56,432	4	0.7	2.9
≥2	968	24,991	2	0.3	1.9
Total	105,444	3,079,502	50	38.0	12.0

[a] Fitted cases are based on the recommended model for the salivary gland cancer.
[b] The person-years and fitted cases shown are rounded; the sum of the numeric totals does not necessarily equal the total in the bottom row.
[c] Background cases are estimates of the expected number of cases among cohort members with no radiation exposure.

attained age (–2.75 power, $P = 0.03$ for attained age alone and –0.76 power, $P > 0.5$ after allowing for effect modification by age at exposure), sex ($P > 0.5$), smoking ($P > 0.5$) or alcohol ($P > 0.5$). The estimated decrease in radiation ERR was 66% per decade increase in age at exposure (95% CI: 32% to 88%) with ERR per Gy estimates of 6.3 (95% CI: 2.3 to 14), 0.72 (95% CI: 0.04 to 3.2) and 0.08 (95% CI: 0.006 to 1.2) at exposure ages 10, 30 and 50, respectively. A linear dose-response model with effect modification by age at exposure and total shielded kerma >4 Gy was selected as a preferred model for salivary gland cancer. A joint analysis indicated statistically significant heterogeneity in radiation effects between oral/pharyngeal cancers other than salivary gland and salivary gland cancers ($P = 0.01$).

Excess cases. Because there was no indication for radiation effect on incidence of oral/pharyngeal cancers other than salivary gland, we calculated the excess cases due to radiation exposure only for salivary gland cancer. We estimate that 12 of 50 observed cases were attributed to radiation (Table 3) based on the fitted preferred model.

Esophageal Cancer

There were 486 esophageal cancers accounting for 2% of all first primary solid cancers ascertained in the LSS during 1958–2009 (*22*). Histological type was known for 81% of the esophageal cancers and virtually all of those with known histology were squamous cell carcinomas (Appendix Table A1, middle part). The location of the tumor was known for almost two thirds of esophageal cancers and of these 77% originated in the upper/middle part of the esophagus.

Baseline rates. Baseline rates for esophageal cancer increased with age, with some indication of a downturn or flattening late in life for males (Supplementary Fig. S2; http://dx.doi.org/10.1667/RR15386.1.S1). Rates were significantly higher among males than females ($P < 0.001$). There was a significant birth cohort effect among males with age-specific rates increasing by approximately 10% per decade increase in year of birth, but no indication of a birth cohort effect among females.

Both smoking history and alcohol consumption had statistically significant effects on the baseline rates when included in the model simultaneously (Supplementary Table S3). Adjustment for these effects reduced, but did not fully explain, the baseline-rate sex difference. While the baseline rates for non-smoking and non-drinking males and females were more similar than the unadjusted rates, the significant differences in the sex-specific age patterns ($P < 0.001$) persisted and there was still evidence of a significant birth cohort effect in males ($P = 0.02$). In the analyses by tumor location, the risks with smoking and alcohol consumption were significant for upper/middle esophageal cancers and insignificant for lower esophageal cancers.

Radiation effects. Under a linear dose-response model, the ERR for esophageal cancer was 0.32 per Gy (95% CI: –0.001 to 0.81, $P = 0.05$). After adjustment for the highly significant effects of smoking and alcohol consumption on the baseline rates, the ERR per Gy increased slightly to 0.36 (95% CI: 0.01 to 0.86). The fit of the simple linear model was significantly improved by the addition of a quadratic term in dose ($P = 0.03$). The quadratic model also fit the data better than the simple linear model and marginally better than the linear-quadratic model, which provided negative estimates for low-dose range. The Akaike Information Criterion (AIC) values for the linear-quadratic and linear models were 0.50 and 3.09 greater than that for the quadratic model. The fitted ERR at 1 Gy for the quadratic model was 0.30 (95% CI: 0.06 to 0.66). Figure 2 shows the fitted dose-response curves together with dose category-specific estimates of the ERR.

Given the sex difference in dose-response curvature seen for all solid cancer in the recent LSS analyses (*22*), we also considered models in which the dose-response shape was allowed to differ for males and females. Relative to a null model with sex-specific linear dose responses, there was statistically significant evidence for curvature in males ($P = 0.01$). A model with a quadratic dose response for males fit slightly worse than the linear-quadratic model ($P = 0.07$). The dose category-specific ERR estimates for females were unstable due to the small number of cases, but there was no evidence of quadratic departure from linearity in the female dose response ($P > 0.5$). These dose-response model

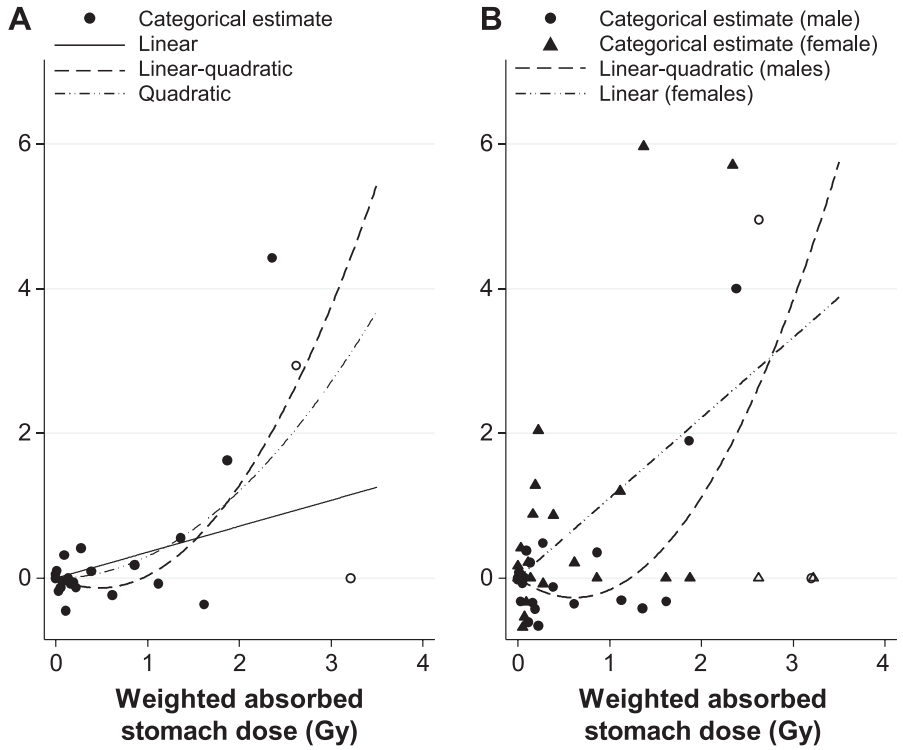

FIG. 2. Esophageal cancer dose response. Plots indicate the esophageal cancer dose response. The estimates in panel A assume a common dose response for males and females while those in panel B show sex-specific dose response. The points are dose-category-specific estimates of the ERR. Open circles and triangles indicate estimates for subjects who were exposed to unshielded kerma <4 Gy. Black lines are the fitted linear (solid), quadratic (dashed) and linear-quadratic (dashed-dotted) dose-response functions. The estimates are adjusted for smoking and alcohol effects.

comparisons and parameter estimates are presented in Appendix Table A2. Based on the AIC values, the preferred dose-response model was linear-quadratic for males and linear for females.

We examined the evidence for effect modification using the preferred ERR model. There was no evidence of statistically significant effects of attained age ($P > 0.5$) or age at exposure ($P > 0.5$), and a model with time since exposure did not converge.

Radiation effects by tumor localization. Examination of esophageal tumors by anatomical sub-site indicated that the ERR was highest for cancers of the lower esophagus, being 0.91 per Gy (95% CI: <0.04 to 2.86, $P = 0.007$, Table 4). The dose-response model for cancer of the lower part of the esophagus was not improved by allowing for a quadratic term in dose ($P = 0.22$). There were no indications of significant radiation effects for cancers of the upper or mid-esophagus ($P > 0.5$). A joint analysis comparing radiation effect estimates for the upper/middle esophagus with those for the lower esophagus indicated that the risks differed significantly ($P = 0.03$). Inclusion of smoking and alcohol consumption had little effect on the estimated radiation effects.

Excess cases. Observed and fitted number of esophageal cancer cases (calculated based on the quadratic ERR model, with smoking history and alcohol consumption modeled as multiplicative joint effects) are shown in Table 5. As mentioned above, the model with the smallest AIC was linear-quadratic for males and linear for females; however, this model provided negative estimates for the number of excess cases in males. With a quadratic dose-response model, there were a total of 11.3 radiation-associated cases. Because of the substantial alcohol and smoking effects and their multiplicative joint effects with radiation, most of these cases (9.6) occurred among men.

Stomach Cancer

Of 5,661 first primary cases of stomach cancer reported in the LSS during 1958–2009, histology was known for 80% of the cases, and almost 99% of those were classified as adenocarcinoma (Appendix Table A1, lower part).

Baseline rates. Like cancers of the oral cavity/pharynx and esophagus, baseline rates of stomach cancer were higher among males than among females, and increased with age with some indication of a downturn or flattening late in life for males (Supplementary Fig. S3; http://dx.doi.org/10.1667/RR15386.1.S1). Both smoking and alcohol consumption had significant effects on stomach cancer rates when analyzed separately. However, after adjustment for smoking history, the effect of alcohol consumption was no

TABLE 4
Parameter Estimates for Esophageal Cancer in Multiplicative Excess Relative Risk Models with Smoking Effects and Alcohol Effects

	Simple linear ERR[a]	Quadratic ERR	Preferred model, adjusted for smoking and alcohol
All esophageal cancer (n = 486)			
ERR/Gy	0.32 (–0.008, 0.80)[b]		
ERR/Gy^2		0.27 (0.04, 0.61)	0.30[c] (0.05, 0.65)
AIC[d]	77.7	75.0	0
Upper and middle esophagus (n = 240)			
ERR/Gy	0.09 (<–0.29, 0.89)		–0.0005[c] (–0.54[e], 0.53[e])
AIC	46.8		0
Lower esophagus (n = 70)			
ERR/Gy	0.91[c] (–0.58[e], 2.86)		1.07 (<0.10, 3.63)
AIC	3.2		0

[a] Excess relative risk.
[b] 95% Confidence interval.
[c] Recommended models are, for esophageal cancer $(1 + \beta d^2 * \exp(\phi I(K > 4)))(1 + ERR_{smk})(1 + ERR_{drk})$, for cancers of the upper and middle esophagus $(1 + \beta d * \exp(\phi I(K > 4)))(1 + ERR_{smk})(1 + ERR_{drk})$ and for cancers of the lower esophagus $(1 + \beta d * \exp(\phi I(K > 4)))$, where d is radiation dose, I is an indication function, K is total shielded kerma, and β and ϕ are regression coefficients.
[d] Akaike Information Criterion (AIC) difference from model with lowest AIC.
[e] Wald-type confidence limit.

longer statistically significant (Supplementary Table S4). Even after adjustment for smoking, the baseline rates in (non-smoking) males were significantly greater than those in females (female versus male ratio: F/M = 0.8, $P < 0.001$).

Radiation effects. The risk of stomach cancer significantly increased with increasing dose under a simple linear model, with an ERR of 0.36 per Gy (Table 6, Fig. 3). The dose-response appeared to be linear (P value for quadratic dose term >0.50). Stomach cancer is the predominant cancer among LSS subjects, however an upward curvature for males, which was significant for all solid cancers combined (*22*), was not significant, but was suggested ($P = 0.08$) in the analysis using a model allowing the curvature to differ for males and females. We investigated factors possibly affecting the dose-response shape using the same approach as Grant *et al*. (*22*). We found that the P value of curvature for males became large in the analyses using DS02 doses (data not shown). Furthermore, if we allowed the female/male ratio of ERR to vary between the subjects with unshielded kerma estimates ≤4 Gy and >4 Gy, the curvature for males appears to be derived from the subjects with unshielded kerma estimates >4 Gy (Supplementary Table S5). We concluded that the linear model is a preferred dose-response model for stomach cancer both in males and females with shielded kerma ≤4 Gy. While smoking was strongly associated with stomach cancer baseline rates, adjustment for smoking had little effect on radiation effect estimates (Table 6). The radiation risk was significantly higher for females (F/M = 2.20, 95% CI: 1.15 to 4.80, $P = 0.02$). In a model allowing for modification by attained age, the radiation effect decreased with increasing attained age

TABLE 5
Observed and Fitted[a] Cancers of the Esophagus by Dose Category for Various Risk Factors

				Fitted values			
Dose (Gy)	People	Person-years[b]	Cases	Total	Background[c]	Non-radiation excess[d]	Radiation excess
<0.005	60,983	1,787,606	276	268.5	81.8	186.7	0.0
–0.1	27,536	808,203	130	130.1	39.1	91.0	0.1
–0.2	5,584	163,606	21	25.9	8.2	17.6	0.2
–0.5	5,931	169,815	29	27.3	8.4	17.9	0.9
–1	3,216	90,718	13	16.7	4.4	9.9	2.4
–2	1,628	44,903	9	12.3	2.1	5.4	4.8
≥2	566	14,642	8	5.2	0.6	1.7	2.9
Total	105,444	3,079,492	486	486.0	144.6	330.2	11.3
Male	42,910	1,142,236	394	394.0	65.7	318.8	9.6
Female	62,534	1,937,256	92	92.0	78.9	11.4	1.7

[a] Fitted cases were based on quadratic multiplicative dose-response model for all esophageal cancers with no sex difference in the risk.
[b] The person-years showed were rounded; the sum of the numeric totals does not necessarily equal the total in lowest row.
[c] Background cases are the expected number of cases in that would be expected on the cohort if there was no smoking, alcohol consumption or radiation exposure.
[d] The estimated number of esophageal cancers associated with alcohol and or smoking. The estimated number of smoking associated cases was 257.3 while 213.8 cases were estimated to be associated with alcohol consumption. N.B. since the estimates are based on a multiplicative model they include each 141.0 cases estimated to be associated with the joint effect of smoking and alcohol intake.

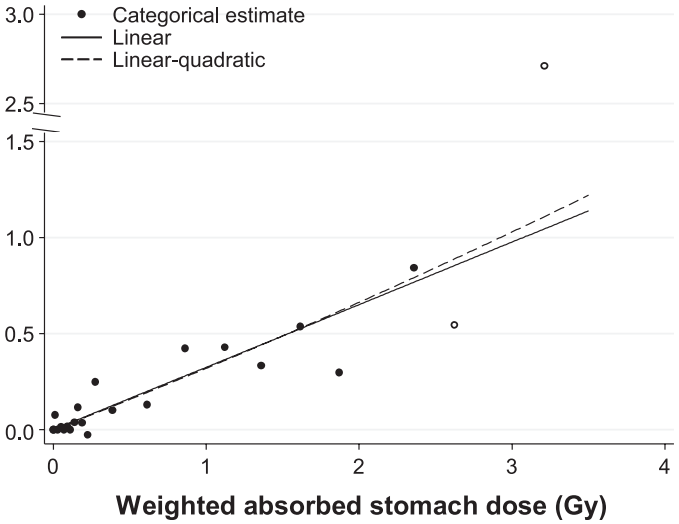

FIG. 3. Dose-response plots for stomach cancer. Fitted linear (solid line) and linear-quadratic (dashed) radiation dose-response functions for stomach cancer show both sexes combined. The plot also includes categorical estimates of the ERR. The open circles show the estimates for subjects who received unshielded kerma >4 Gy.

($P = 0.003$). Allowing sex-dependent attained age effects did not improve model fit (P value for sex difference of attained age effect = 0.46). While effect modification by age at exposure was marginally significant when considered on its own ($P = 0.05$), its addition to the model allowing for effect modification by attained age was no longer significant ($P = 0.32$). These results were similar to those of the previously published cancer incidence study by Preston *et al*. (*4*). The sex-averaged ERR estimates based on the preferred model (a linear ERR model with effect modification by attained age and total shielded kerma, with multiplicative joint effect with smoking history) were 0.62 per Gy (95% CI: 0.40 to 0.88) and 0.33 per Gy (95% CI: 0.20 to 0.47) at ages 50 and 70 years, respectively.

The sex-averaged excess absolute risk (EAR) at age 70 was 9.86 cases per 10,000 person-years per Gy. The EAR increased significantly with attained age (1.75 power of attained age, 95% CI: 0.72 to 2.92, $P < 0.001$), while there was no effect of age at exposure ($P = 0.80$) in the model allowing for the effect modification by attained age. The sex ratio of EAR for stomach cancer was almost unity ($P = 0.29$).

Analyses by anatomical parts of the stomach. We performed separate analyses of three stomach cancer sub-sites: gastric cardia cancers (n = 341), cancers of the upper/middle stomach (n = 1,253) and cancers of the lower stomach (n = 1,501). A statistically significant dose response was seen for each of these sub-sites with little evidence for heterogeneity in the ERR per Gy estimates (data not shown). Although smoking effects were observed for each of these sub-sites, adjustment for smoking using a multiplicative joint effects model had no appreciable effect on the radiation risk estimates. There were no indications of significant radiation effect modification by attained age, age at exposure or sex for cancers of gastric cardia or cancers of the lower stomach. The radiation effect for cancers of upper/middle stomach decreased significantly with increasing attained age ($P < 0.001$) but this effect did not significantly vary by sex ($P = 0.30$).

Excess cases. Table 7 shows the observed and fitted number of stomach cancer cases calculated based on the preferred ERR model. Despite a clear association between smoking and stomach cancer, the estimated number of excess cases attributed to smoking was only 474 cases (8%). A total of 178 stomach cancer cases (3%) of 5,661 observed cases were estimated as radiation-related cancers based on the fitted model.

DISCUSSION

We investigated radiation effects on first primary cancer incidence in the upper digestive tract (oral cavity/pharynx, esophagus and stomach) in a fixed cohort of atomic bomb survivors with 52 years of follow-up, 11 years more than in the previously reported studies. As a result of the extended follow-up period, the number of oral cavity/pharyngeal and

TABLE 6
Parameter Estimates for Stomach Cancer in Multiplicative Excess Relative Risk Models and Excess Absolute Risk Model with Adjustment for Smoking

All stomach cancers (n = 5,661)					
	Excess relative risk (ERR)			Excess absolute risk (EAR)	
	Simple linear ERR	Linear ERR adjusted for smoking	Linear model with effect modifiers, adjusted for smoking		Linear model with effect modifiers, adjusted for smoking
ERR/Gy	0.36 (0.22, 0.50)[a]	0.33 (0.20, 0.47)	0.33[b] (0.20, 0.47)	EAR/Gy	9.16 (5.14, 14.0)
Attained age (power)	-	-	–1.93 (–2.94, –0.82)	Attained age (power)	1.75 (0.72, 2.92)
Sex ratio (F/M)	-	-	2.20 (1.15, 4.80)	Sex ratio (F/M)	1.06 (0.50, 3.02)
AIC[c]	115.3	15.1	0		

[a] 95% Confidence interval.

[b] Recommended model, stomach cancer $\left(1 + \beta_s d * \exp\left(\delta_1 \log\left(\frac{a}{70}\right) + \phi I(K > 4)\right)\right)(1 + ERR_{smk})$, where d is radiation dose, I is an indication function, a is attained age, K is total shielded kerma, and β, δ and ϕ are regression coefficients.

[c] Akaike Information Criterion (AIC) difference from model with lowest AIC.

TABLE 7
Observed and Fitted[a] Cancers of the Stomach by Dose Category for Various Risk Factors

Dose (Gy)	People	Person-years[b]	Cases	Background[c]	Radiation[d]	Smoking[b]
<0.005	60,983	1,787,606	3,156	2,923.3	0.6	253.0
–0.1	27,536	808,203	1,490	1,291.2	16.6	133.9
–0.2	5,584	163,606	301	272.1	15.8	28.1
–0.5	5,931	169,815	340	281.3	37.1	30.3
–1	3,216	90,718	205	147.8	42.5	16.5
–2	1,628	44,903	118	72.2	39.8	9.5
≥2	566	14,642	51	21.2	25.8	2.7
Total	105,444	3,079,492	5,661	5,009.1	178.1	473.8

[a] Fitted cases were based on multiplicative models for the joint effects of radiation and smoking on the risk of stomach cancers.
[b] The person-years and fitted cases shown are rounded; the sum of the numeric totals does not necessarily equal the total on the bottom row.
[c] Background cases are estimates of the expected number of cases among non-smoking cohort members with no radiation exposure.
[d] The excess cases for radiation include cases associated with the interaction between radiation and smoking.

esophageal cancers increased by 40%, while the number of stomach cancers increased by 20%. In site-specific analyses, we considered the effects of smoking and alcohol consumption on the baseline rates and radiation risks. For each site, we have provided more detailed analyses of radiation dose-response and effect modification than previously reported work, i.e., including smoking and alcohol consumption as well as age, sex and time since exposure. Across all sites, adjustment for smoking history and alcohol consumption had almost no impact on the estimated excess risks due to radiation. We have also highlighted the difference in the radiation effects for salivary gland cancers and cancers in other parts of the oral cavity/pharynx, and considered esophageal and stomach cancer risks by anatomical location. In general, the updated results are consistent with the site-specific findings of earlier reports.

The relatively large increases in the number of oral cavity/pharyngeal and esophageal cancers during the recent follow-up period are consistent with trends observed for rates in the Japanese population-based cancer registry study (*29*), which suggests increasing age-standardized rates for these cancers. The smaller increase, compared to previous years, in the number of stomach cancer cases is also consistent with the declining incidence of stomach cancer in Japan (*30*).

Oral cavity/pharyngeal cancers collectively showed significant association with radiation. However, the evidence for a radiation effect was derived almost completely from the striking radiation effect on the risk of salivary gland cancers, while there was virtually no evidence of a radiation effect for other cancers of the oral cavity/pharynx. The salivary gland cancer risks are consistent with those reported by Land *et al.* (*31*) based on 41 cases diagnosed between 1950 and 1987. The contrast between radiation effects on salivary gland and other oral cavity cancer rates is also consistent with results reported by Thompson *et al.* (*32*). The radiation ERR for salivary gland cancer decreased rapidly with increasing age at exposure. Only three of the sixteen cases among survivors with doses of 100 mGy or more were more than 20 years old at the time of exposure. The lack of cases among those who were exposed at older ages may be due to chance or due to the low baseline incidence of salivary gland cancer, but the results suggest that radiation effects on salivary gland cancer risk for people exposed as adults is likely to be low.

The esophageal cancer dose response appears to be non-linear with upward curvature, particularly for men. While this pattern is consistent with the finding of significant curvature in the male all solid cancer dose response noted in our recently reported LSS work (*22*), the esophagus is one of the few individual cancer sites in the LSS with evidence of significant non-linearity in the radiation dose response. In some studies of radiotherapy patients, significant risk for esophageal cancer has been reported (*3, 33–35*), while in others this has not been the case (*36, 37*). Significantly increased esophageal cancer risk from exposure to low-dose radiation was observed in the study of nuclear facility workers (*38*) and the Techa River Cohort (*6*). Dose-response shapes were not considered in these studies. The number of cases in the current study limited our ability to describe the shape of the dose response precisely.

The analysis by anatomical sub-site in the esophagus showed significant radiation risk only for the lower esophagus and no radiation-related increase in risk for the upper/middle esophagus. In contrast, the risks due to alcohol consumption and smoking were significant for the upper/middle esophagus and insignificant for the lower esophagus. In Western societies, incidence rates of lower-esophageal adenocarcinoma have been rapidly increasing since the late 1990s (*39*), possibly as a consequence of increased rates of Barrett's esophagus. However, squamous cell carcinoma remains dominant in Japan and drastic increase of esophageal adenocarcinoma rates similar to those in Western societies has not been observed (*40*). Among cancers of the lower esophagus in the current study, there were only four adenocarcinomas and eight with unknown morphology (most of which are likely to be squamous cancers since they were diagnosed prior to 1980). The observed difference between the radiation effects on

cancers of the upper/middle and lower esophagus is unlikely to be a consequence of errors in histological type or misclassification of stomach cancers.

Among the registered cases, detailed anatomical location was unknown for 34% of esophageal and 31% of stomach cancers (Appendix Table A3). More than 55% of esophageal or stomach cancers diagnosed before 1975 were registered without detailed information for morphology and topography. The percentage of cancers of the lower esophagus in earlier years more than doubled that in later years. There are possibilities that the observed significant radiation risk only for the lower part of the esophagus might result from misclassification of stomach cardia cancer in the early period. However, before 1975 the percentage of cardia cancer among stomach cancers with known topography was not low compared to that after 1975 (6%) and a majority of cases for which topography was known had known morphologies, as well. The possibility of misclassification between esophageal and stomach cancer is likely to be low.

Stomach cancer is the most common cancer among Japanese men [age standardized incidence rate (ASR) 45.8/100,000 person-years] and the third most common cancer among Japanese women (ASR 16.5/100,000 person-years) (*15*). Not surprisingly, it accounts for more than 25% of solid cancers observed in the LSS. While an excess risk of stomach cancer has been observed in cancer survivors after receiving high-dose radiation treatment for cancers of the cervix (*11*), testes (*12*) and non-Hodgkin lymphoma (*13*), and in patients irradiated for benign conditions (*3, 14*), risk estimates from the LSS provide the most convincing evidence for radiation-related risk of stomach cancer at low-to-moderate doses, and form the major source of human data used for establishing radiation safety standards.

In this study, the dose response for stomach cancer appeared to be linear for females and the limited evidence for a non-linear dose response for males was largely eliminated after we allowed the effect of shielded kerma ($\leq$4 Gy and $>$4 Gy) on the ERR to differ in females and males. This was not the case for esophageal cancer, for which there was marked evidence for curvature in the male dose response even when the dose range was restricted to survivors with doses of less than 2 Gy or even less than 1 Gy. The results of Grant *et al*. also indicated marked curvature in the male solid cancer dose response over dose ranges up to 2 Gy (*22*). While the curvature in the male esophageal cancer dose response might contribute to the curvature observed for all solid cancer, it appears likely that a combination of different factors might be involved, not limited to variations in the shape of the site-specific radiation dose responses, including potential misspecification of the background rates and effect modification in the combined analysis of all solid cancers.

Smoking and alcohol consumption were associated with excess risk of upper digestive cancers. Inclusion of these variables as multiplicative risk factors significantly improved model fit, but had little impact on radiation risk estimates. These data provide no indications of significant modification of the radiation ERR by smoking or alcohol. However, the power to detect smoking or alcohol-related effect modification associated with departures from the multiplicative ERR models considered in these analyses is limited.

In summary, we estimated radiation risks for upper digestive cancers, including cancers of the oral cavity/pharynx, esophagus and stomach, among atomic bomb survivors based on the follow-up period during 1958 to 2009. The results are largely consistent with the results of prior analyses in this cohort. The three sites, oral cavity/pharynx, esophagus and stomach, showed significant increases in cancer risk with radiation dose. Explicit adjustment for lifestyle factors had almost no impact on the radiation risk estimates for any site. The esophageal cancer dose response for males exhibited significant upward curvature, while there was no evidence of significant non-linearity in the dose response for esophageal cancers for females or for other upper digestive tract cancers for either males or females. In view of the relatively large proportion of the LSS cohort exposed at young ages who were alive at the end of 2009, further follow-up is likely to provide additional insights into the nature of the radiation effects on upper digestive tract cancers, especially those of the oral cavity/pharynx and esophagus.

SUPPLEMENTARY INFORMATION

Table S1. Parameter estimates of smoking and/or alcohol consumption for upper digestive tract cancers in the multiplicative excess relative risk model for oral cavity/pharyngeal cancers other than salivary gland cancer.

Table S2. Parameter estimates of smoking and/or alcohol consumption for upper digestive tract cancers in the multiplicative excess relative risk model for salivary gland cancer.

Table S3. Parameter estimates of smoking and/or alcohol consumption for upper digestive tract cancers in the multiplicative excess relative risk model for esophageal cancer.

Table S4. Parameter estimates of smoking and/or alcohol consumption for upper digestive tract cancers in the multiplicative excess relative risk model for stomach cancer.

Table S5. Parameter estimates of radiation dose terms and comparison of model fitting by handling of subjects with $>$ 4Gy kerma.

Fig. S1. Background incidence rates of oral cavity/pharyngeal cancer excluding salivary gland cancer.

Fig. S2. Background incidence rates of esophageal cancer, with and without adjustment for smoking and alcohol.

Fig. S3. Background incidence rates of stomach cancer, with and without adjustment for smoking and alcohol.

TABLE A1
Distribution of Cases by Morphology and Topography

Site	Topographical codes	Morphology				
		Squamous cell carcinoma	Adenocarcinoma	Other	NOS[a]	Total
Oral cavity/pharynx						
Salivary gland	ICD-O-1 142; ICD-O-2,3 C07-08	7	29	9	5	50
Oral cavity	140-141, 143-145; C00-06	197	15	8	12	232
Pharyngeal	146-148; C09-13	93	0	1	13	107
Other/unspecified	149; C14	3	0	0	2	5
Total		300	44	18	32	394
Esophagus						
Upper/middle	1500, 1501, 1503, 1504; C150-151, C153-154	221	1	2	16	240
Lower	1502, 1505; C152, C155	58	4	0	8	70
Other/unspecified	1508-1509; C158-159	105	0	2	69	176
Total		384	5	4	93	486
Stomach						
Cardia	1510; C160	2	282	9	48	341
Upper/middle	1514, C162	1	1,188	14	50	1,253
Lower	1511, 1512; C163, C164	0	1,381	4	116	1,501
Other/unspecified	1519; C169	1	1,598	21	946	2,566
Total		4	4,449	48	1,160	5,661

[a] Not otherwise specified.

TABLE A2
Comparison of Linear, Quadratic and Linear-Quadratic (LQ) Esophageal Cancer Dose-Response Models in Males and Females

Dose response				ERR parameter estimates			
				Males		Females	
Model	n[a]	*P*	AIC[b]	Linear	Quadratic	Linear	Quadratic
None	0	-	3.79	-	-	-	-
Common linear	1	0.04[c]	3.71	0.36 (0.01, 0.86)	-	0.36[d]	-
Common quadratic	1	0.01[c]	0.63	-	0.30 (0.06, 0.66)	-	0.30[d]
Common LQ	2	0.22[e]/0.03[f]	1.13	–0.57 (–1.3, 0.38)	0.60 (0.05, 1.24)	–0.57[d]	0.60[d]
Male linear; female linear	2	0.24[g]	4.33	0.27 (–0.06, 0.77)	-	1.09 (–0.1, 3.18)	-
Male LQ; female linear	3	0.07[e]/0.01[f]	0	–0.88 (–1.7, 0.08)	0.72 (0.15, 1.39)	1.11 (–0.02, 3.10)	-
Male quadratic; female linear	2	-	1.26	-	0.26 (0.02, 0.62)	1.11 (–0.02, 3.13)	-

[a] Number of parameters related radiation effects.
[b] Akaike Information Criterion (AIC) difference from model with lowest AIC (LQ for male and linear for female dose response).
[c] *P* value for evaluating the null hypothesis of no dose response.
[d] These models assumed common dose response for male and females. Estimates are common with those for males.
[e] *P* value for evaluating whether the linear term is 0.
[f] *P* value for evaluating whether the quadratic term is 0.
[g] *P* value for evaluating for sex difference in linear dose response.

TABLE A3
Distribution of Esophageal Cancer (left) and Stomach Cancer (right) by Anatomical Sites and Year of Diagnosis

Esophageal cancer					Stomach cancer				
	Period					Period			
	1958–1975	1976–1992	1993–2009	Total		1958–1975	1976–1992	1993–2009	Total
Upper	6	5	12	23	Cardia	134	108	99	341
%	4.32	3.73	5.63	4.73	%	6.62	5.54	5.86	6.02
Middle	24	72	121	217	Upper/middle	186	466	601	1,253
%	17.27	53.73	56.81	44.65	%	9.19	23.91	35.60	22.13
Lower	31	15	24	70	Lower	375	625	501	1,501
%	22.30	11.19	11.27	14.40	%	18.53	32.07	29.68	26.51
Other	1	6	6	13	Other	201	351	243	795
%	0.72	4.48	2.82	2.67	%	9.93	18.01	14.40	14.04
NOS[a]	77	36	50	163	NOS	1,128	399	244	1,771
%	55.40	26.87	23.47	33.54	%	55.73	20.47	14.45	31.28
Total	139	134	213	486	Total	2,024	1,949	1,688	5,661
%	100.00	100.00	100.00	100.00	%	100.00	100.00	100.00	100.00

[a] Not otherwise specified.

APPENDIX

Table A1. Distribution of cases by morphology and topography.

Table A2. Comparison of linear, quadratic and linear-quadratic esophageal cancer dose-response models in males and females.

Table A3. Distribution of esophageal cancer (left side) and stomach cancer (right side) by anatomical sites and year of diagnosis.

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